

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 413/12, A61K 31/41, C07D 453/02, 413/14		A1	(11) International Publication Number: WO 95/30675
			(43) International Publication Date: 16 November 1995 (16.11.95)
(21) International Application Number: PCT/EP95/01578 (22) International Filing Date: 25 April 1995 (25.04.95) (30) Priority Data: 9409061.0 6 May 1994 (06.05.94) GB 9409068.5 6 May 1994 (06.05.94) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): GASTER, Laramie, Mary [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). WYMAN, Paul, Adrian [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). (74) Agent: SUMMERSELL, Richard, John; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).			(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.
(54) Title: BIPHENYLCARBOXAMIDES USEFUL AS 5-HT _{1D} ANTAGONISTS			
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(i)</p> </div> <div style="text-align: center;"> <p>(ii)</p> </div> </div>			
(57) Abstract <p>Compounds of formula (I), processes for their preparation and their use as CNS agents through 5HT_{1D} receptor antagonism are disclosed, in which A is CONR where R is hydrogen or C₁-alkyl; B is oxygen, S(O)_q where q is 0, 1 or 2, or B is NR¹⁰ where R¹⁰ is hydrogen or C₁-alkyl or B is CH₂ when R⁷ and R form a group D; R¹ is hydrogen, halogen, C₁-alkyl, C₃-cycloalkyl, COC₁-alkyl, C₁-alkoxy, hydroxy, hydroxyC₁-alkyl, hydroxyC₁-alkoxy, C₁-alkoxyC₁-alkoxy, acyl, nitro, trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR^{10R11}, CO₂R¹⁰, CONR^{10R11}, CO₂NR^{10R11}, CONR¹⁰(CH₂)_aCO₂R¹¹, (CH₂)_aNR^{10R11}, (CH₂)_aCONR^{10R11}, (CH₂)_aNR¹⁰COR¹¹, (CH₂)_aCO₂C₁-alkyl, CO₂(CH₂)_aOR¹⁰, NR^{10R11}, NR¹⁰CO₂R¹¹, NR¹⁰CONR^{10R11}, CR¹⁰=NOR¹¹, CNR¹⁰=NOR¹¹, where R¹⁰ and R¹¹ are independently hydrogen or C₁-alkyl and a is 1 to 4 or R¹ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; R² and R³ are independently hydrogen, halogen, C₁-alkyl, C₃-cycloalkyl, C₃-cycloalkenyl, C₁-alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO₂R¹¹, CONR^{12R13}, NR^{12R13} where R¹¹, R¹² and R¹³ are independently hydrogen or C₁-alkyl; R⁴ and R⁵ are independently hydrogen or C₁-alkyl; R⁶ is hydrogen, halogen, hydroxy, C₁-alkyl or C₁-alkoxy; R⁷ is hydrogen or together with R forms a group D where D is CR¹⁴=CR¹⁵, CR¹⁴=CR¹⁵CR^{14R15} or (CR^{14R15})_b where b is 2 or 3 and R¹⁴ and R¹⁵ are independently hydrogen or C₁-alkyl; m is 0, 1, 2, or 3; n is 1 or 2; and R⁸ is a group of formula (i) where p, q and r are independently integers having the value 1, 2 or 3; or R⁸ is a group of formula (ii) where s is 0, 1, 2 or 3 and R¹⁶ is hydrogen or C₁-alkyl.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

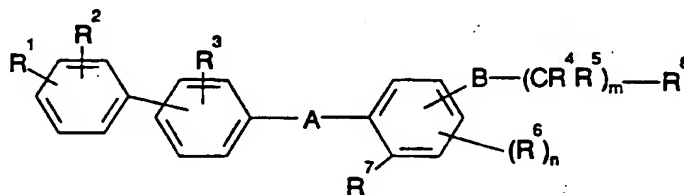
AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

BIPHENYLCARBOXAMIDES USEFUL AS 5-HT_{1D} ANTAGONISTS

The present invention relates to novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

- 5 EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess 5HT_{1D} receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders.

A structurally distinct class of compounds have now been discovered and have been found to exhibit 5HT_{1D} antagonist activity. In a first aspect, the present invention
10 therefore provides a compound of formula (I) or a salt thereof:



(I)

15

in which

A is CONR where R is hydrogen or C₁₋₆alkyl;

B is oxygen, S(O)_q where q is 0, 1 or 2, or B is NR¹⁰ where R¹⁰ is hydrogen or C₁₋₆alkyl or B is CH₂ when R⁷ and R form a group D;

- 20 R¹ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, acyl, nitro, trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹⁰R¹¹, CO₂R¹⁰, CONR¹⁰R¹¹, CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)_aCO₂R¹¹, (CH₂)_aNR¹⁰R¹¹, (CH₂)_aCONR¹⁰R¹¹, (CH₂)_aNR¹⁰COR¹¹, (CH₂)_aCO₂C₁₋₆alkyl, CO₂(CH₂)_aOR¹⁰, NR¹⁰R¹¹,
25 NR¹⁰CO₂R¹¹, NR¹⁰CONR¹⁰R¹¹, CR¹⁰=NOR¹¹, CNR¹⁰=NOR¹¹, where R¹⁰ and R¹¹ are independently hydrogen or C₁₋₆alkyl and a is 1 to 4 or R¹ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R² and R³ are independently hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl,

- 30 C₃₋₆cycloalkenyl, C₁₋₆alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO₂R¹¹, CONR¹²R¹³, NR¹²R¹³ where R¹¹, R¹³ and R¹³ are independently hydrogen or C₁₋₆alkyl;

R⁴ and R⁵ are independently hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen, halogen, hydroxy, C₁₋₆alkyl or C₁₋₆alkoxy;

- 35 R⁷ is hydrogen or together with R forms a group D where D is CR¹⁴=CR¹⁵, CR¹⁴=CR¹⁵CR¹⁴R¹⁵ or (CR¹⁴R¹⁵)_b where b is 2 or 3 and R¹⁴ and R¹⁵ are

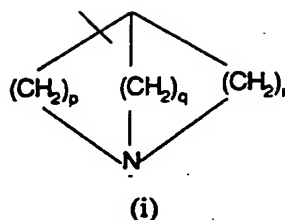
independently hydrogen or C₁₋₆alkyl;

m is 0, 1, 2 or 3;

n is 1 or 2; and

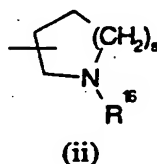
R⁸ is a group of formula (i):

5



where p, q and r are independently integers having the value 1, 2 or 3;

10 or R⁸ is a group of formula (ii):



15 where s is 0, 1, 2 or 3 and R¹⁶ is hydrogen or C₁₋₆alkyl.

C₁₋₆alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably R¹ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, hydroxC₁₋₆alkyl, hydroxC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, acyl, nitro, trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹⁰R¹¹, CO₂R¹⁰, 20 CONR¹⁰R¹¹, CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)_aCO₂R¹¹, (CH₂)_aNR¹⁰R¹¹, (CH₂)_aCONR¹⁰R¹¹, (CH₂)_aNR¹⁰COR¹¹, (CH₂)_aCO₂C₁₋₆alkyl, CO₂(CH₂)_aOR¹⁰, NR¹⁰R¹¹, NR¹⁰CO₂R¹¹, NR¹⁰CONR¹⁰R¹¹, CR¹⁰=NOR¹¹, CNR¹⁰=NOR¹¹, where R¹⁰ and R¹¹ are independently hydrogen or C₁₋₆alkyl and a is 1 to 4 or R¹ is an 25 optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Examples of suitable heterocyclic rings include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl. These heterocyclic rings can be linked to the remainder of the molecule via a carbon atom or, when present, a nitrogen 30 atom. Optional substituents for such rings include R² and R³ groups defined above, preferred substituents include C₁₋₆alkyl. Preferably R¹ is oxadiazolyl, most preferably a 5-methyl-1,2,4-oxadiazol-3-yl group.

Suitably R^2 and R^3 are independently hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{1-6} alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{11} , $CONR^{12}R^{13}$, $NR^{12}R^{13}$ where R^{11} , R^{12} and R^{13} are independently hydrogen or C_{1-6} alkyl. Preferably R^2 is C_{1-6} alkyl, in particular methyl.

5 Preferably R^3 is hydrogen.

Suitably R^4 and R^5 are independently hydrogen or C_{1-6} alkyl. Preferably R^4 and R^5 are both hydrogen.

Suitably R^6 is hydrogen, halogen, hydroxy, C_{1-6} alkyl or C_{1-6} alkoxy. Preferably R^6 is C_{1-6} alkoxy such as methoxy.

10 Suitably R^7 is hydrogen or C_{1-6} alkyl, preferably R^7 is hydrogen.

Suitably R^8 is a group of formula (i) or (ii). When R^8 is a group of formula (i) p, q and r are preferably 2. Preferably R^8 is a group of formula (ii) where s is 1 and R^{16} is C_{1-6} alkyl such as methyl.

Suitably A is $CONR$ where R is hydrogen or C_{1-6} alkyl, that is to say A forms an amide linkage. Preferably A is $CONR$ where R is hydrogen. Suitably R^7 together with R forms a group D where D is $CR^{14}=CR^{15}$, $CR^{14}=CR^{15}CR^{14}R^{15}$ or $(CR^{14}R^{15})_b$ where b is 2 or 3 and R^{14} and R^{15} are independently hydrogen or C_{1-6} alkyl. Preferably R^{14} and R^{15} are both hydrogen. Preferably D is an ethyl linkage, that is to say forms part of an indoline ring.

20 Suitably B is oxygen, $S(O)_q$ where q is 0, 1 or 2, or B is NR^{10} where R^{10} is hydrogen or C_{1-6} alkyl or B is CH_2 when R^7 and R form a group D. Preferably B is oxygen.

Suitably m is 0, 1, 2 or 3, preferably m is 1.

Suitably n is 1 or 2, preferably n is 1.

25 The groups



and R^6 can be attached to the phenyl ring at any suitable position.

Preferably the group



30 is meta to the amide linkage and the group R^6 is para to the amide linkage. The groups R^1 , R^2 and R^3 can be attached at any suitable position.

Particularly preferred compounds of the invention include:

N-[3-((S)-1-Methylpyrrolidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

35 N-[4-Methoxy-3-((R)-1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[4-Methoxy-3-((R)-pyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-

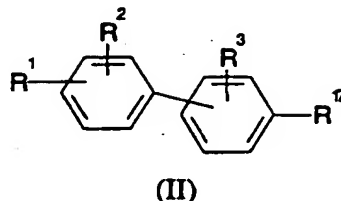
- oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(1-methylazetidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[3-(Azetidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 5 N-[4-Methoxy-3-(1-methylpiperidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(1-methylazepin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 10 N-[4-Methoxy-3-(1-methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(1-methylpiperidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(1-methylpyrrolidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 15 N-[4-Methoxy-3-(3-quinuclidinyloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(quinuclidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 20 N-[4-Chloro-3-(1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-(1-Methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 5-Chloro-2,3-dihydro-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(1-methylpyrrolidin-2-ylmethoxy)-1H-indole,
 25 2,3-Dihydro-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-[2-(1-methylpyrrolidin-2-yl)ethyl]-1H-indole,
 and pharmaceutically acceptable salts thereof.

- Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

- Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomers of compounds of formula (I) and mixtures thereof also form an aspect of the invention.

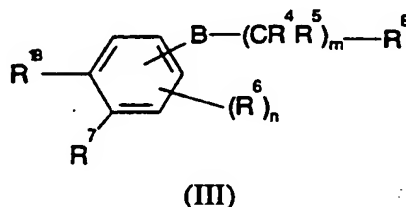
In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) for compounds where A is an amide linkage CONR^9 reaction of a compound of formula (II):



5

with a compound of formula (III):

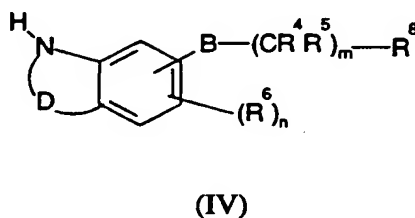


10

wherein B, m, n, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as defined in formula (I) and R^{17} and R^{18} contain the appropriate functional group(s) necessary to form the A moiety; or

(b) where R^7 together with R^9 forms a group D reaction of a compound of formula (II) as defined above with a compound of formula (IV):

15



20

wherein B, D, m, n, R^4 , R^5 , R^6 and R^8 are as defined in formula (I); and optionally after (a) or (b) in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

25

Suitably R^{17} is an activated carboxylic acid derivative, such as an acyl halide or acid anhydride, and R^{18} is an amine group. Activated compounds of formulae (II) or (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphoryl azole. Preferably R^{17} is a group COL where L is halo, particularly chloro.

30

A compound of formulae (II) and (III) are typically reacted together in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide, triethylamine or pyridine.

Compounds of formula (II) and (IV) are reacted together using similar reaction
5 conditions to those for compounds (II) and (III).

Intermediate compounds of formulae (II), (III) and (IV) are commercially available or can be prepared using standard procedures such as those outlined in EPA 533266/7/8. Certain intermediate compounds of formulae (II) to (IV) are novel and form a further aspect of the invention.

10 It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

15 Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

Certain compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures.

20 5HT_{1D} Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia,
25 amnesic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

30 5HT_{1D} Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, the present invention, provides a compound of general formula (I) or a
35 physiologically acceptable salt or solvate thereof for use in therapy.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In another aspect the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

5 In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

10 In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

15 The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20 A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

25 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

30 Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

35 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and

buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Description 1**2-((S)-1-Methylpyrrolidin-2-ylmethoxy)-4-nitroanisole**

A stirred solution of 2-methoxy-5-nitrophenol (1.0g, 0.0059 mol) and (S)-(-)-1-methylpyrrolidine-2-methanol (0.70 ml, 0.0059 mol) in dry THF (60 ml) was treated at room temperature under argon with triphenylphosphine (1.57g, 0.0060 mol), followed by diethyl azodicarboxylate (0.94 ml, 0.0060 mol). A slight exotherm occurred. The solution was stirred at room temperature for 24 h, then concentrated under vacuum. The residue was treated with 1M HCl acid and ethyl acetate, shaken well and the aqueous layer separated, basified with potassium carbonate and extracted with ethyl acetate. The extract was dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow oil, which was approx. 70% title compound (1.2g). This was used crude in the next stage.

¹H NMR (250 MHz; CDCl₃) δ (ppm): 7.92 (dd, 1H), 7.77 (d, 1H), 6.90 (d, 1H), 4.03 (dd, 2H), 3.95 (s, 3H), 3.18-3.07 (m, 1H), 2.83-2.73 (m, 1H), 2.53 (s, 3H), 2.39-2.27 (m, 1H), 2.14-2.02 (m, 1H), 1.95-1.66 (m, 3H).

Description 2**4-Methoxy-3-((S)-1-methylpyrrolidin-2-ylmethoxy) aniline**

A solution of 2-((S)-1-methylpyrrolidin-2-ylmethoxy)-4-nitroanisole (D1, 1.8g of 70% purity) in ethanol (8 ml) was hydrogenated over 10% Pd-C (0.5g) at atmospheric pressure and temperature until uptake of hydrogen ceased. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo* to leave a light purple oil (1.6g), which was approx. 70% title compound. This was used crude in the next stage.

¹H NMR (250 MHz; CDCl₃) δ (ppm): 6.70 (d, 1H), 6.32 (d, 1H), 6.23 (dd, 1H), 4.02-3.95 (m, 1H), 3.90-3.80 (m, 1H), 3.78 (s, 3H), 3.15-3.04 (m, 1H), 2.79-2.68 (m, 1H), 2.49 (s, 3H), 2.36-2.24 (m, 1H), 2.12-2.00 (m, 1H), 1.90-1.65 (m, 3H).

Description 3**(R)-1-tert-Butoxycarbonylpyrrolidin-2-ylmethanol**

A stirred solution of (R)-pyrrolidine-2-methanol (0.5g, 5.0 mmol) and triethylamine (0.81 ml, 5.8 mmol) in dichloromethane (20 ml) was treated with a solution of di-tert-butyl dicarbonate (1.08g, 5.0 mmol) in dichloromethane (10 ml). The mixture was stirred at room temp. for 1 h, then treated with 10% Na₂CO₃ solution (20 ml) and extracted with dichloromethane. The extract was dried (Na₂SO₄) and concentrated *in vacuo* to afford the

title compound as a colourless oil (1.0g, 100%).

¹H NMR (250 MHz, CDCl₃) δ(ppm): 4.78 (br d, 1H), 4.05-3.93 (m, 1H), 3.68-3.55 (m, 2H), 3.52-3.40 (m, 1H), 3.38-3.26 (m, 1H), 2.10-1.94 (m, 1H), 1.90-1.70 (m, 3H), 1.48 (s, 9H).

Description 4

2-((R)-1-tert-Butoxycarbonylpyrrolidin-2-ylmethoxy)-4-nitroanisole

10 A stirred solution of 2-methoxy-5-nitrophenol (0.84g, 5.0 mmol), triphenylphosphine (1.28g, 5.0 mmol) and (R)-1-tert-butoxycarbonylpyrrolidin-2-ylmethanol (D3, 1.0g, 5.0 mmol) in THF (30 ml) at room temp. under argon was treated with diethyl azodicarboxylate (0.77 ml, 5.0 mmol). A slight exotherm occurred. The mixture was stirred for 2 h, then concentrated *in vacuo* and the residue treated with 10% Na₂CO₃ solution and extracted with ethyl acetate. The extract was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 1:1 ether/60-80 petrol to afford the title compound as a yellow solid (1.25g, 71%).

20 ¹H NMR (200 MHz, CDCl₃) δ(ppm): 7.98-7.70 (m, 2H), 6.90 (br d, 1H), 4.30-4.12 (m, 2H), 4.08-3.90 (m, 1H), 3.94 (s, 3H), 3.52-3.25 (m, 2H), 2.15-1.70 (m, 4H), 1.48 (s, 9H).

Description 5

3-((R)-1-tert-Butoxycarbonylpyrrolidin-2-ylmethoxy)-4-methoxyaniline

25 The title compound was prepared from 2-((R)-1-tert-butoxycarbonylpyrrolidin-2-ylmethoxy)-4-nitroanisole (D4) using the procedure of Description 2, as a pale purple oil (88%).

30 ¹H NMR (200 MHz, CDCl₃) δ(ppm): 6.65 (br d, 1H), 6.50-6.10 (m, 2H), 4.20-4.00 (m, 2H), 3.90-3.60 (m, 1H), 3.70 (s, 3H), 3.40-3.20 (m, 2H), 3.0-2.2 (v br, 2H), 2.15-1.65 (m, 4H), 1.40 (s, 9H).

Description 6

4-Methoxy-3-((R)-1-methylpyrrolidin-2-ylmethoxy)aniline

35 A solution of 3-((R)-1-tert-butoxycarbonylpyrrolidin-2-ylmethoxy)-4-methoxyaniline (D5, 0.61g, 1.9 mmol) in THF (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.14g, 3.8 mmol) in THF (20 ml) at room temperature under argon,

then heated under reflux for 1.5h. The mixture was cooled, then treated cautiously with water (0.15 ml), followed by 10% NaOH solution (0.15 ml), followed by water (0.45 ml). The mixture was filtered through a pad of kieselguhr and the filtrate concentrated *in vacuo* to afford the title compound as a pink oil (0.34g, 76%).

5

¹H NMR (200 MHz, CDCl₃) δ (ppm): 6.72 (d, 1H), 6.34 (d, 1H), 6.23 (dd, 1H), 4.05-3.94 (m, 1H), 3.90-3.78 (m, 1H), 3.78 (s, 3H), 3.45 (br s, 2H), 3.17-3.03 (m, 1H), 2.78-2.63 (m, 1H), 2.50 (s, 3H), 2.38-2.20 (m, 1H), 2.18-1.95 (m, 1H), 1.90-1.65 (m, 3H).

10 Description 7

N-[3-((R)-1-tert-Butoxycarbonylpyrrolidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

The title compound was prepared from 3-((R)-1-tert-butoxycarbonyl-pyrrolidin-2-ylmethoxy)-4-methoxyaniline (D5) using the procedure of Example 1. Purification by chromatography on silica gel eluting with 50-100% ether/60-80 petrol afforded the title compound as a pale yellow oil (58%)

¹H NMR (200 MHz, CDCl₃) δ (ppm): 8.35-8.15 (m, 1H), 8.07-7.88 (m, 4H), 7.50-7.10 (m, 5H), 6.87 (d, 1H), 4.30-4.10 (m, 2H), 4.00-3.75 (m, 1H), 3.85 (s, 3H), 3.50-3.25 (m, 2H), 2.68 (s, 3H), 2.34 (s, 3H), 2.20-1.75 (m, 4H), 1.46 (s, 9H).

25 Description 8

1-tert-Butoxycarbonylazetidin-2-ylmethanol

25

A stirred suspension of lithium aluminium hydride (0.25g, 6.5 mmol) in THF (50 ml) at room temp. under argon was treated portionwise with 2-azetidinecarboxylic acid (0.50g, 4.9 mmol), then heated under reflux for 2h followed by 5 days at room temp. The mixture was treated cautiously with water (0.25 ml), followed by 10% NaOH solution (0.25 ml), followed by water (0.75 ml). The mixture was filtered through kieselguhr and the filtrate treated with triethylamine (0.74 ml, 5.3 mmol) and di-tert-butyl dicarbonate (1.06g, 4.9 mmol), then stirred at room temp. for 2 h. The solution was concentrated *in vacuo* and the residue treated with 10% Na₂CO₃ solution and extracted with dichloromethane. The extract was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a colourless oil (0.90g, 98%)

35

¹H NMR (200 MHz, CDCl₃) δ (ppm): 4.55-4.35 (br m, 1H), 4.2 (br s, 1H), 3.96-3.62 (m, 4H), 2.30-2.08 (m, 1H), 2.05-1.80 (m, 1H), 1.45 (s, 9H).

Description 9**2-(1-tert-Butoxycarbonylazetidin-2-ylmethoxy)-4-nitroanisole**

- 5 The title compound was prepared from 1-tert-butoxycarbonylazetidin-2-ylmethanol (D8) and 2-methoxy-5-nitrophenol using the procedure of Description 4 (100%).

¹H NMR (250 MHz, CDCl₃) δ(ppm): 8.2-7.8 (m, 2H), 7.10-6.86 (m, 1H), 4.60-3.90 (m, 8H), 2.50-2.25 (m, 1H), 1.46 (s, 9H). 1 other H not discernable from spectrum.

10

Description 10**3-(1-tert-Butoxycarbonylazetidin-2-ylmethoxy)-4-methoxyaniline**

- 15 The title compound was prepared from 2-(1-tert-butoxycarbonylazetidin-2-ylmethoxy)-4-nitroanisole (D9) using the procedure of Description 2 (100%). This material was used in the next step without purification.

Description 11**4-Methoxy-3-(1-methylazetidin-2-ylmethoxy)aniline**

20

The title compound was prepared from 3-(1-tert-butoxycarbonylazetidin-2-ylmethoxy)-4-methoxyaniline (D10) using the procedure of Description 6 (85%).

- 25 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.70 (d, 1H), 6.33 (d, 1H), 6.23 (dd, 1H), 3.98 (d, 2H), 3.76 (s, 3H), 3.60 (br s, 2H), 3.52-3.37 (m, 2H), 2.92-2.75 (m, 1H), 2.40 (s, 3H), 2.15-1.95 (m, 2H).

Description 12

- 30 N-[3-(1-tert-Butoxycarbonylazetidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 35 The title compound was prepared from 3-(1-tert-butoxycarbonylazetidin-2-ylmethoxy)-4-methoxyaniline (D10) using the procedure of Example 1. Purification by chromatography on silica gel eluting with 0-30% ethyl acetate/ether afforded the title compound as a pale yellow oil (51%).

¹H NMR (200 MHz, CDCl₃) δ (ppm): 8.32 (s, 1H), 8.03-7.90 (m, 4H), 7.48-7.15 (m, 5H), 6.87 (d, 1H), 4.60-4.45 (m, 1H), 4.35-4.10 (m, 2H), 3.95-3.78 (m, 2H), 3.83 (s, 3H),

2.68 (s, 3H), 2.40-2.22 (m, 2H), 2.32 (s, 3H), 1.40 (s, 9H).

Description 13

1-Methyl-3-(2-methoxy-5-nitrophenoxy)azepine (A)

5 **and 1-Methyl-2-(2-methoxy-5-nitrophenoxy)methyl)piperidine (B)**

A stirred solution of 2-methoxy-5-nitrophenol, (3.50g, 0.021 mol), triphenylphosphine (5.43g, 0.021 mol) and 1-methyl-2-piperidine methanol (2.71 ml, 0.021 mol) under argon was cooled to 0°C and diethyl azodicarboxylate (3.26 ml, 0.021 mol) was then added
10 slowly to the stirred solution. The mixture was then allowed to warm to room temperature and was stirred for 1h before being evaporated under reduced pressure. The residue was then partitioned between chloroform and 5M HCl. The organic layer was then washed with 5M HCl (1X) and the combined aqueous layers were then treated with solid sodium hydrogen carbonate until pH8 was reached. The resultant suspension was then extracted
15 with CHCl₃ (3X) and the combined organic layers were then dried (Na₂SO₄) and evaporated under reduced pressure to give a yellow solid. The solid was purified by silica gel chromatography (9385, 1→2.5% MeOH/CH₂Cl₂ as eluant) to give the title compound (A) as a colourless oil (1.36g, 23%), followed by the title compound (B) (0.203g, 3%) as a colourless oil.

20

¹H NMR (400 MHz, CDCl₃), (A) δ (ppm): 7.90 (dd, 1H), 7.78 (d, 1H), 6.90 (d, 1H), 4.52 (m, 1H), 3.91 (s, 3H), 2.92 (dd, 1H), 2.82 (dd, 1H), 2.68 (m, 1H), 2.58 (m, 1H), 2.41 (s, 3H), 2.18 (m, 1H), 1.90 (m, 1H), 1.75 (m, 3H), 1.60 (m, 1H).

25

¹H NMR (250 MHz, CDCl₃) (B) δ (ppm): 7.91 (dd, 1H), 7.72 (d, 1H), 6.90 (d, 1H), 4.15 (dd, 1H), 4.05 (dd, 1H), 3.93 (s, 3H), 2.90 (m, 1H), 2.40 (s, 3H), 2.20 (m, 1H), 1.80 (m, 3H), 1.70-1.20 (m, 4H).

Description 14

30 **4-Methoxy-3-(1-methylpiperidin-2-ylmethoxy)aniline**

1-Methyl-2-(2-methoxy-5-nitrophenoxy)methyl)piperidine (D13B, 0.203g, 0.725 mmol) was converted according to the method of description 2 to give the title compound as a brown oil that crystallised on standing (0.170g, 94%)

35

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.70 (d, 1H), 6.30 (d, 1H), 6.22 (dd, 1H), 4.12 (dd, 1H), 3.90 (dd, 1H), 3.78 (s, 3H), 3.30 (br s, 2H), 2.92 (m, 1H), 2.40 (s, 3H), 2.20 (m, 1H), 1.92-1.25 (m, 7H).

Description 15**4-Methoxy-3-(1-methylazepin-3-yloxy)aniline**

- 5 1-Methyl-3-(2-methoxy-5-nitrophenoxy)azepine (D13A, 0.231g, 0.825 mmol) was converted according to the method of description 2 to give the **title compound** as a brown oil (0.195g, 95%).

10 ^1H NMR (250 MHz, CDCl_3) δ (ppm): 6.70 (d, 1H), 6.40 (d, 1H), 6.25 (dd, 1H), 4.50 (m, 1H), 3.78 (s, 3H), 3.70 (br s, 2H), 3.10 (m, 1H), 2.85 (m, 2H), 2.50 (s, 3H), 2.20 (m, 1H), 2.12 (m, 1H), 2.00-1.55 (m, 5H).

Description 16**1-Methyl-3-(2-methoxy-5-nitrophenoxyethyl)piperidine**

- 15 2-Methoxy-5-nitrophenol (0.350g, 2.07 mmol) and 1-methylpiperidine-3-methanol (0.27g, 2.07 mmol) were converted to the **title compound** as a pale yellow oil (0.126g, 22%) according to the method of description 13.

20 ^1H NMR (250 MHz, CDCl_3) δ (ppm): 7.91 (dd, 1H), 7.70 (d, 1H), 6.90 (d, 1H), 3.95 (s, 3H), 3.93 (m, 2H), 3.00 (m, 1H), 2.80 (m, 1H), 2.30 (s, 3H), 2.20 (m, 1H), 2.10 (m, 5H), 1.15 (m, 1H).

Description 17

- 25 **4-Methoxy-3-(1-methylpiperidin-3-ylmethoxy)aniline**

30 1-Methyl-3-(2-methoxy-5-nitrophenoxyethyl)piperidine (D16, 0.125g, 0.446 mmol) was converted to give the **title compound** as a colourless oil (0.084g, 75%) according to the method of description 2.

35 ^1H NMR (250 MHz, CDCl_3) δ (ppm): 6.70 (d, 1H), 6.30 (d, 1H), 6.20 (d, 1H), 3.82 (dd, 2H), 3.79 (s, 3H), 3.40 (br s, 2H), 3.00 (m, 1H), 2.78 (m, 1H), 2.30 (s, 3H), 2.20 (m, 1H), 2.05-1.55 (m, 5H), 1.10 (m, 1H).

Description 18**1-Methyl-3-(2-methoxy-5-nitrophenoxy)piperidine**

2-Methoxy-5-nitrophenol (0.732g, 4.33 mmol) and 1-methylpiperidin-3-ol (0.50g, 4.33 mmol) were converted to the title compound as a pale yellow oil (0.098g, 9%) according to the method of description 13.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.91 (dd, 1H), 7.81 (d, 1H), 6.92 (d, 1H), 4.42 (m, 1H), 3.90 (s, 3H), 3.00 (m, 1H), 2.68 (m, 1H), 2.30 (s, 3H), 2.29-2.02 (m, 3H), 1.88 (m, 1H), 1.62 (m, 2H)

Description 19**4-Methoxy-3-(1-methylpiperidin-3-yloxy)aniline**

1-Methyl-3-(2-methoxy-5-nitrophenoxy)piperidine (D18, 0.098g, 0.368 mmol) was converted accordingly to the method of description 2 to give the title compound as a colourless oil (0.070g, 81%)

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.65 (d, 1H), 6.32 (d, 1H), 6.19 (dd, 1H), 4.20 (m, 1H), 3.70 (s, 3H), 3.30 (br s, 2H), 3.00 (m, 1H), 2.60 (m, 1H), 2.22 (s, 3H), 2.00 (m, 3H), 1.75 (m, 1H), 1.65-1.30 (m, 2H).

Description 20**1-Methyl-3-(2-methoxy-5-nitrophenoxy)pyrrolidine**

25

The title compound (1.2g, 50%) was prepared as a pale oil from 1-methyl-3-pyrrolinol (1.09 ml, 0.01 mole) and 2-methoxy-5-nitrophenol (1.6g, 0.01 mole), using the method of Description 13.

¹H NMR (200 MHz; CDCl₃) δ (ppm): 7.91 (dd, 1H), 7.65 (d, 1H), 6.91 (d, 1H), 5.00-4.84 (br s, 1H), 3.94 (s, 3H), 3.00-2.79 (m, 3H), 2.61-2.31 (m, 5H), 2.17-1.94 (m, 1H).

Description 21**4-Methoxy-3-(1-methylpyrrolidin-3-yloxy)aniline**

35

The title compound (0.90g, 81%) was prepared as a light brown solid from 1-methyl-3-(2-methoxy-5-nitrophenoxy)pyrrolidine (D20, 1.2g, 0.005 mol), using the method of

Description 2.

¹H NMR (250 MHz, d⁶DMSO) δ (ppm): 6.65 (d, 1H), 6.28 (s, 1H), 6.07 (d, 1H), 4.98-4.26 (br s, 2H), 3.70-2.99 (m, 4H), 2.86-2.08 (m, 8H), 1.89-1.55 (m, 1H).

5

Description 22**4-Nitro-2-(3-quinuclidinyloxy)anisole**

The title compound was prepared from 2-methoxy-5-nitrophenol and 3-quinuclidinol using the procedure of Description 1. Purification by chromatography on silica gel eluting with 5% methanol/chloroform afforded a beige solid (22%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.92 (dd, 1H), 7.67 (d, 1H), 6.94 (d, 1H), 4.53-4.43 (m, 1H), 3.97 (s, 3H), 3.42-3.28 (m, 1H), 3.12-2.70 (m, 5H), 2.25-2.16 (m, 1H), 2.12-1.94 (m, 1H), 1.87-1.70 (m, 1H), 1.68-1.52 (m, 1H), 1.50-1.34 (m, 1H).

15

Description 23**4-Methoxy-3-(3-quinuclidinyloxy)aniline**

The title compound was prepared from 4-nitro-2-(3-quinuclidinyloxy) anisole (D22) using the procedure of Description 2 (78%).

¹H NMR (200 MHz, CDCl₃) δ (ppm): 6.65 (d, 1H), 6.23-6.10 (m, 2H), 4.30-4.18 (m, 1H), 3.70 (s, 3H), 3.50 (br s, 2H), 3.25-3.08 (m, 1H), 3.05-2.55 (m, 5H), 2.15-1.90 (m, 2H), 1.75-1.55 (m, 1H), 1.54-1.20 (m, 2H)

25

Description 24**4-Nitro-2-(quinuclidin-2-ylmethoxy)anisole**

The title compound, was prepared using a procedure similar to that given in Description 1, using 2-methoxy-5-nitrophenol (2g, 0.012mol) and quinuclidin-2-ylmethanol (Beugt. Langström, *Chemica Scripta*, 1974, 5, 170) (1.67g, 0.012 mol) to give a yield of 1.52g, (53%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.92 (1H, dd), 7.80 (1H, d), 6.90 (1H, d), 4.22-4.18 (1H, m), 3.92 (4H, m), 3.38 (1H, m), 2.98-2.72 (4H, m), 1.9-1.78 (2H, m), 1.62-1.5 (4H, m), 1.40-1.23 (1H, m).

35

Description 25**4-Methoxy-3-(quinuclidin-2-ylmethoxy)aniline**

A procedure similar to that given in Description 2 was used to give the title compound
5 (1.15g, 84%) from 4-nitro-2-(quinuclidin-2-ylmethoxy) anisole (D24).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.70 (1H, d), 6.35 (1H, d), 6.25 (1H, dd), 4.08
(1H, m), 3.85 (1H, m), 3.78 (3H, s), 3.30 (2H, m), 2.98 (4H, m), 2.80 (1H, m), 1.85-1.79
(2H, m), 1.60-1.47 (4H, m), 1.42-1.20 (1H, m).

10

Description 26**2-(1-tert-Butoxycarbonylpyrrolidin-2-ylmethoxy)-1-chloro-4-nitrobenzene**

A stirred solution of pyrrolidine-2-methanol (425 mg) in dichloromethane (24 ml) was
15 treated at 0° C with triethylamine (1.16 ml) followed by a solution of di-
t-butylidicarbonate (1.51g) in dichloromethane (10 ml). After warming to room temperature
over 1h, the mixture was washed with 10% Na₂CO₃ and the organic phase was dried
(Na₂SO₄). The solvent was evaporated under reduced pressure to give a colourless oil
(1.37g), which was dissolved in dry tetrahydrofuran (40 ml) and treated at room
20 temperature with 2-chloro-5-nitrophenol (1.17g), triphenylphosphine (1.77g) and diethyl
azodicarboxylate (1.06 ml). The mixture was stirred overnight at room temperature under
argon, the solvent was evaporated under reduced pressure and the residue partitioned
between 10% Na₂CO₃ and ethyl acetate. The organic phase was dried (Na₂SO₄), and the
solvent evaporated under reduced pressure to give the crude product which was purified
25 by chromatography on silica gel, eluting with 60°-80° petroleum ether and diethyl ether,
to afford the title compound. (1.25g, 50%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.89-7.74 (m, 2H), 7.58-7.48 (m, 1H), 4.3-4.01
(m, 3H), 3.55-3.31 (m, 2H), 2.2-2.04 (m, 3H), 1.98-1.83 (m, 1H), 1.49 (s, 9H).

30

Description 27**2-(2-Chloro-5-nitrophenoxymethyl)pyrrolidine**

A solution of 2-(1-tert-butoxycarbonylpyrrolidin-2-ylmethoxy)-1-chloro-4-nitrobenzene
35 (D26) (700 mg) in dichloromethane (80 ml) was treated with trifluoroacetic acid (10 ml)
and stirred at room temperature for 2h, then basified with NaHCO₃. The organic phase
was separated and dried (Na₂SO₄), and the solvent evaporated under reduced pressure to
give the title compound as a pale yellow waxy solid. (500 mg, 99%).

¹H NMR (200 MHz, CDCl₃) δ (ppm): 9.55 (brs, 1H), 7.9-7.69 (m, 2H), 7.51 (d, 1H), 4.51-4.26 (m, 2H), 4.24-4.05 (m, 1H), 3.56-3.28 (m, 2H), 2.45-1.99 (m, 4H).

5 Description 28

2-(2-Chloro-5-nitrophenoxyethyl)-1-methylpyrrolidine

A stirred solution of 2-(2-chloro-5-nitrophenoxyethyl)pyrrolidine (D27) (780 mg) in formic acid (16 ml) was treated with formaldehyde solution (37-40% in 85:15 H₂O: Methanol) (0.31 ml) and heated to reflux for 3 h, then allowed to stand overnight at room temperature. The solvents were evaporated under reduced pressure and the residue partitioned between Na₂CO₃ and ethyl acetate. The organic phase was dried (Na₂SO₄) and the solvent evaporated under reduced pressure to leave the title compound as a pale yellow solid. (317 mg, 60%).

15

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.82-7.75 (m, 2H), 7.5 (d, 1H), 4.05 (d, 2H), 3.14 (t, 1H), 2.88-2.78 (m, 1H), 2.55 (s, 3H), 2.41-2.3 (m, 1H), 2.18-1.65 (m, 4H).

Description 29

20 4-Chloro-3-(1-methylpyrrolidin-2-ylmethoxy)aniline

A solution of 2-(2-chloro-5-nitrophenoxyethyl)-1-methylpyrrolidine (D28) (832 mg) in ethanol (18 ml) was warmed to 60° and treated with a solution of stannous chloride (2.33g) in concentrated hydrochloric acid (18 ml), then heated to reflux for ½ h. The reaction mixture was cooled, diluted with water and basified with 10% NaOH, then extracted with chloroform. The organic phase was dried (Na₂SO₄) and the solvent evaporated under reduced pressure to give the title compound as a brown oil. (661 mg, 89%).

30 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.09 (d, 1H), 6.28 (s, 1H), 6.2 (d, 1H), 3.99-3.82 (m, 2H), 3.66 (br s, 2H), 3.1 (t, 1H), 2.8-2.68 (m, 1H), 2.51 (s, 3H), 2.38-2.25 (m, 1H), 2.15-2.0 (m, 1H), 1.94-1.63 (m, 3H)

Description 30

35 1-Methyl-3-(4-nitrophenoxyethyl)piperidine

1-Methyl-3-piperidinemethanol (2.0g, 0.016 mole) in dry DMF (50 ml) was added dropwise to a suspension of sodium hydride (0.51g of an 80% dispersion in oil, 0.017

mole) in dry DMF (20 ml) under argon and the mixture stirred for 0.5 h. 1-Fluoro-4-nitrobenzene (2.4g, 0.018 mole) in dry DMF (20 ml) was added dropwise and the mixture stirred at ambient temperature for 18 h. Water was added dropwise until effervescence ceased and the mixture extracted into Et₂O. The combined Et₂O layers were extracted into 5N HCl, basified with 40% NaOH solution, extracted into Et₂O, dried (Na₂SO₄) and evaporated *in vacuo*. The resulting yellow oil was flash columned on silica gel eluting with 5% EtOH/CHCl₃ to leave the title compound (1.32g, 33%) as a pale yellow oil.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.20 (d, 2H), 6.95 (d, 2H), 4.03-3.84 (m, 2H), 2.93 (brd, 1H), 2.78 (brd, 1H), 2.71 (s, 3H), 2.27-2.10 (m, 1H), 2.09-1.55 (m, 5H), 1.25-1.02 (m, 1H).

Description 31

4-(1-Methylpiperidin-3-ylmethoxy)aniline

The title compound was prepared from 1-methyl-3-(4-nitrophenoxyethyl) piperidine (D30) using the method of Description 2.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.73 (d, 2H), 6.62 (d, 2H), 3.89-3.59 (m, 2H), 3.53 (br s, 2H), 3.00 (br d, 1H), 2.82 (br d, 1H), 2.33 (s, 3H), 2.26-2.06 (m, 1H), 2.05-1.57 (m, 5H), 1.18-0.99 (m, 1H)

Description 32

N-(2,2-Dimethoxyethyl)-4-chloro-3-(1-methylpyrrolidin-2-ylmethoxy)aniline

A stirred solution of 4-chloro-3-(1-methylpyrrolidin-2-ylmethoxy)aniline (D29, 1.8g) in methanol (40 ml) and glacial acetic acid (2.15 ml) was treated with 2,2-dimethoxyethanal (2.3g of approx 40% solution in methyl tert-butyl ether). The solution was cooled to 0°C and treated portionwise with sodium cyanoborohydride (2.36g), then allowed to warm to room temperature over 2 h. The mixture was basified with 10% NaOH solution and extracted with dichloromethane. The organic extract was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a brown oil (2.25g, 92%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.10 (d, 1H), 6.21 (s, 1H), 6.15 (d, 1H), 4.55 (t, 1H), 4.01-3.80 (m, 3H), 3.41 (s, 6H), 3.21 (t, 2H), 3.10 (t, 1H), 2.81-2.70 (m, 1H), 2.55 (s, 3H), 2.39-2.28 (m, 1H), 2.15-1.99 (m, 1H), 1.91-1.65 (m, 3H)

Description 33**5-Chloro-6-(1-methylpyrrolidin-2-ylmethoxy)-1H-indole**

- A solution of N-(2,2-dimethoxyethyl)-4-chloro-3-(1-methylpyrrolidin-2-ylmethoxy)aniline (D32) (1.5g) in trifluoroacetic acid (5.8 ml) at 0° C under argon, was treated dropwise with trifluoroacetic anhydride (5.8 ml) and stirring continued at 0° C for a further 0.5 h. A further quantity of trifluoroacetic acid (8.5 ml) was added and the mixture heated at reflux for 7 h, then allowed to stand overnight at room temperature. The solvents were evaporated under reduced pressure, and the residue was partitioned between 10% Na₂CO₃ and ethyl acetate. The organic phase was dried (Na₂SO₄) and the solvent evaporated under reduced pressure to give the crude indole which was chromatographed on silica gel eluting with methanol and chloroform to give the title compound (375 mg, 31%)
- ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.57 (br s, 1H), 7.6 (s, 1H), 7.15-7.09 (m, 1H), 6.92 (s, 1H), 6.44-6.39 (m, 1H), 4.11-3.89 (m, 2H), 3.27-3.12 (m, 1H), 2.95-2.77 (m, 1H), 2.61 (s, 3H), 2.49-2.3 (m, 1H), 2.2-1.68 (m, 4H)

Description 34**5-Chloro-2,3-dihydro-6-(1-methylpyrrolidin-2-ylmethoxy)-1H-indole**

- A solution of 5-chloro-6-(1-methylpyrrolidin-2-ylmethoxy)-1H-indole (D33) (375 mg) in glacial acetic acid (9 ml) was treated with sodium cyanoborohydride (0.42g) at room temperature, with stirring. After 1h, the reaction mixture was partitioned between 40% NaOH and dichloromethane. The organic phase was dried (Na₂SO₄) and the solvent evaporated under reduced pressure. The crude indoline was chromatographed on alumina eluting with ethyl acetate, to give the title compound as a pale yellow oil (201 mg, 53%).
- ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.02 (s, 1H), 6.29 (s, 1H), 4.0-3.8 (m, 2H), 3.55 (t, 2H), 3.1 (t, 1H), 2.95 (t, 2H), 2.79-2.65 (m, 1H), 2.51 (s, 3H), 2.37-2.2 (m, 1H), 2.12-2.0 (m, 1H), 1.9-1.65 (m, 3H)

Description 35**2-(2-Methoxyphenethyl)-1-pyrroline**

- A stirred solution of diisopropylamine (49 ml, 0.35 mole) in dry ether (1000 ml) at -60° C under argon was treated over 10 minutes with 1.6 M n-butyllithium in hexane (200 ml, 0.32 mole) and the resulting solution maintained at -60° C for 15 minutes. This solution

was then treated dropwise over 10 minutes with a solution of 1-trimethylsilylpyrrolidin-2-one (D.H. Hua et al, J. Org. Chem., 1990, 55, 3682) (53.4g, 0.34 mole) in dry ether (150 ml) and the mixture stirred for 15 minutes, then treated dropwise over 10 minutes with a solution of ethyl

- 5 (2-methoxyphenyl)propionate (Y. Tamaru et al, Tet. Lett., 1986, 27, 955) (56g, 0.27 mole) in dry ether (100 ml). The reaction mixture was allowed to warm to room temperature and stir for 20 h, then concentrated *in vacuo*. The residue was treated with 5M HCl (800 ml) and heated under reflux for 20 h, then the solution concentrated *in vacuo* to about 200 ml volume. The aqueous mixture was basified by addition of solid K₂CO₃ and then extracted with ethyl acetate. The extract was dried (Na₂SO₄) and concentrated
10 *in vacuo* to afford the title compound as a brown oil (51.7g, 94%).

- ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.25-7.13 (m, 2H), 6.93-6.82 (m, 2H), 3.88-3.77 (m, 2H), 3.82 (s, 3H), 2.98-2.88 (m, 2H), 2.68-2.56 (m, 2H), 2.54-2.42 (m, 2H), 1.87
15 (quintet, 2H).

Description 36

2-(2-(Pyrrolidin-2-yl)ethyl)anisole

- 20 A stirred solution of 2-(2-methoxyphenethyl)-1-pyrroline (D35, 30g, 0.15 mole) in ethanol (300 ml) at 0° C under argon was treated portionwise over 15 minutes with sodium borohydride (2.8 g, 0.074 mole). Additional sodium borohydride was added after 2 h (1.5g, 0.040 mole) and after a further 1h (1.0g, 0.027 mole). The mixture was allowed to warm to room temperature and stir for 18 h, then cooled to 0° C and treated with 2M HCl
25 until gas effervescence ceased. The mixture was concentrated *in vacuo* and the residue treated with excess 10% Na₂CO₃ solution and extracted with ethyl acetate. The extract was dried and concentrated *in vacuo* to afford the title compound as a brown oil (29.1g, 97%)
- 30 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.22-7.12 (m, 2H), 6.92-6.80 (m, 2H), 3.81 (s, 3H), 3.10-2.92 (m, 2H), 2.90-2.77 (m, 1H), 2.68 (t, 2H), 2.1 (br s, 1H), 2.00-1.60 (m, 5H), 1.38-1.20 (m, 1H).

Description 37

- 35 2-(2-(1-Ethoxycarbonylpyrrolidin-2-yl)ethyl)anisole

A stirred solution of 2-(2-(pyrrolidin-2-yl)ethyl)anisole (D36, 28.5g, 0.139 mol) in dichloromethane (350 ml) at 0° C under Ar was treated with triethylamine (25.2 ml, 0.181

mol) and then ethyl chloroformate (14 ml, 0.139 mol). The mixture was stirred at room temperature for 24 hours, then treated with water (300 ml) and the mixture acidified to pH 2 using 5M HCl. The organic layer was separated, dried (Na₂SO₄) and then concentrated *in vacuo* to afford the title compound as a brown oil (33g, 86%)

5

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.19 (m, 2H), 6.88 (m, 2H), 4.10 (t, 2H), 3.83 (bs, 1H), 3.81 (s, 3H), 3.39 (bs, 2H), 2.60 (t, 2H), 1.85 (m, 5H), 1.60 (m, 1H), 1.22 (t, 3H).

10 Description 38

2-(2-(1-Ethoxycarbonylpyrrolidin-2-yl)ethyl)-4-nitroanisole

A stirred solution of 2-(2-(1-ethoxycarbonylpyrrolidin-2-yl)ethyl)anisole (D37) (2.16 mg, 7.8 mmol) in acetic anhydride (25 ml) under Ar was treated over a period of 10 minutes with copper (II) nitrate trihydrate (2.45 g, 10.1 mmol). The reaction mixture was stirred at room temperature for 2 hours, and then added to saturated aqueous K₂CO₃ solution (200 ml), and treated with 0.880 ammonia solution (70 ml). This mixture was then extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford a brown oil (2.85g) containing the title compound together with the 6-nitro isomer (~50% by NMR). This was used without purification in the next step.

Description 39

3-(2-(1-Ethoxycarbonylpyrrolidin-2-yl)ethyl)-4-methoxyaniline

25

2-(2-(1-Ethoxycarbonylpyrrolidin-2-yl)ethyl)-4-nitroanisole as a mixture with the 6-nitro isomer (D38, 15g, 0.047 mol) in ethanol (300 ml) was hydrogenated over 10 % palladium/charcoal (4 g) at room temperature and atmospheric pressure for 48 hours. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo* to afford a brown oil. This was chromatographed on silica gel, eluting with 1:1 ethyl acetate/petroleum ether (b.p. 60-80° C) to afford the title compound as a brown oil (6.52g, 48%).

30

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.70-6.45 (m, 3H), 4.10 (m, 2H), 3.25 (bs, 1H), 3.22 (s, 3H), 3.37 (bs, 2H), 2.50 (t, 2H), 2.19-1.70 (m, 5H), 1.58 (m, 1H), 1.25 (m, 3H)

35

Description 40**4-Methoxy-3-(2-(1-methylpyrrolidin-2-yl)ethyl)aniline**

3-(2-(1-Ethoxycarbonylpyrrolidin-2-yl)ethyl)-4-methoxyaniline (D39) (3.43g, 0.012 mol) in tetrahydrofuran (60 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.20g, 0.032 mol) in tetrahydrofuran (170 ml) at 0° C under Ar. The mixture was heated to reflux for 2 hours, then cooled and treated with water (1.2 ml), 10% NaOH solution (1.2 ml) and water (3.6 ml) and filtered through kieselguhr. The filtrate was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a brown oil (1.83g, 67%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.75-6.40 (m, 3H), 3.75 (s, 3H + m, 1H), 3.60-3.18 (bs, 2H), 3.08 (t, 1H), 2.31 (s, 3H), 2.72-1.38 (m, 9H)

Description 41**N-(2,2-Dimethoxyethyl)-4-methoxy-3-(2-(1-methylpyrrolidin-2-yl)ethyl)aniline**

4-Methoxy-3-(2-(1-methylpyrrolidin-2-yl)ethyl)aniline (D40) (1.83g, 7.8 mmol) in ethanol (60 ml) was treated with a solution of dimethoxyacetaldehyde in methyl tert-butyl ether (2.65g, 10.0 mmol (~40% solution)). The resulting solution was hydrogenated over 10% palladium/charcoal (0.65g) at atmospheric temperature and pressure for 48 hours. Catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo* to afford a brown oil. The reaction was incomplete, so the brown oil in ethanol (80 ml) was treated with further dimethoxyacetaldehyde (3.93g) and hydrogenated over 10% palladium-charcoal (0.9g) at atmospheric temperature and pressure for 72 hours. Work up as above afforded a brown oil, which was dissolved in ethyl acetate (100 ml) and washed with water (2 x 100 ml). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a brown oil (1.94g, 77%).

¹H NMR (200 MHz, CDCl₃) δ (ppm): 6.70 (d, 1H), 6.50 (m, 2H), 4.55 (t, 1H), 3.72 (s, 3H), 3.58-3.25 (s, 6H + m, 3H), 3.20 (d, 2H), 3.05 (t, 1H), 2.55 (m, 2H), 2.30 (s, 3H), 2.00 (m, 2H), 1.70 (m, 2H), 1.20 (m, 2H).

Description 42**5-Methoxy-6-(2-(1-methylpyrrolidin-2-yl)ethyl)-1H-indole**

The title compound (0.17g, 11%) was prepared as a brown oil from N-(2,2-dimethoxyethyl)-4-methoxy-3-(2-(1-methylpyrrolidin-2-yl)ethyl)aniline (D41) (1.94g, 6.0

mmol) using the method of Description 33.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 8.40 (bs, 1H), 7.15 (s, 1H), 7.10 (m, 1H), 7.03 (s, 1H), 6.42 (m, 1H), 3.85 (s, 3H), 3.09 (m, 3H), 2.85-2.40 (m, 4H), 2.31 (s, 3H), 2.22-1.89 (m, 4H)

Description 43

2,3-Dihydro-5-methoxy-6-(2-(1-methylpyrrolidin-2-yl)ethyl)-1H-indole

- 10 The title compound (0.13 g, 76%) as a brown oil was prepared from 5-methoxy-6-(2-(1-methylpyrrolidin-2-yl)ethyl)-1H-indole (D42) (0.17g, 0.7 mmol) using the method of Description 34, and used without purification in the next step.

Example 1

- 15 N-[3-((S)-1-Methylpyrrolidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- A stirred suspension of 2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (EP 0533268 A1) (300mg, 1.0 mmol) in dichloromethane (15 ml) was treated with oxalyl chloride (0.13 ml, 1.5 mmol) followed by DMF (1 drop) and stirred at room temperature for 2h. The solution was then concentrated *in vacuo* to leave the acid chloride as a yellow solid. This was dissolved in dichloromethane (5 ml) and added to a stirred solution of 4-methoxy-3-((S)-1-methylpyrrolidin-2-ylmethoxy)aniline (D2, 260mg of 70% purity, 1.1 mmol) and triethylamine (0.35 ml, 2.5 mmol) in dichloromethane (15 ml) at room temperature under argon. After 5h, the solution was treated with 10% Na₂CO₃ solution and extracted with dichloromethane. The extract was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 5% methanol/chloroform and the required product further purified by passage through a short basic alumina column eluting with ethyl acetate. The title compound crystallised from ethyl acetate/60-80 petrol (35 mg) as a white solid mp 147-148° C.

- ¹H NMR (250 MHz; CDCl₃) δ (ppm): 8.14 (s, 1H), 8.04-7.89 (m, 4H), 7.48 (d, 1H), 7.42 (d, 2H), 7.31 (d, 1H), 7.10 (dd, 1H), 6.83 (d, 1H), 4.08-3.89 (m, 2H), 3.83 (s, 3H), 3.13-3.03 (m, 1H), 2.80-2.65 (m, 1H), 2.67 (s, 3H), 2.49 (s, 3H), 2.31 (s, 3H), 2.32-2.22 (m, 1H), 2.10-1.95 (m, 1H), 1.90-1.63 (m, 3H).

Example 2

N-[4-Methoxy-3-((R)-1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 5 The title compound was prepared from 4-methoxy-3-((R)-1-methylpyrrolidin-2-ylmethoxy)aniline (D6) using the procedure of Example 1. Purification by chromatography on silica gel eluting with 5% methanol/chloroform followed by crystallisation from ethyl acetate/60-80 petrol afforded the title compound as a white solid (12%) m.pt. 150-151° C.

10

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.02 (s, 1H), 7.98-7.88 (m, 3H), 7.86 (s, 1H), 7.50-7.42 (m, 3H), 7.35 (d, 1H), 7.08 (dd, 1H), 6.87 (d, 1H), 4.10-3.92 (m, 2H), 3.85 (s, 3H), 3.15-3.04 (m, 1H), 2.80-2.70 (m, 1H), 2.68 (s, 3H), 2.51 (s, 3H), 2.34 (s, 3H), 2.35-2.24 (m, 1H), 2.12-2.00 (m, 1H), 1.92-1.65 (m, 3H).

15

Example 3

N-[4-Methoxy-3-((R)-pyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide hydrochloride

- 20 A solution of N-[3-((R)-1-tert.-butoxycarbonylpyrrolidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (D7, 0.30g, 5.0 mmol) in methanol (5 ml) was treated with 1M HCl in ether (5 ml, 5.0 mmol) and stirred at room temp. for 20 h. The solution was concentrated *in vacuo* and the residue crystallised from acetone to afford the title compound as a white solid (0.14g, 52%), m.pt. 190-191° C.

25

- ¹H NMR (250 MHz, d⁶DMSO) δ: (ppm): 10.30 (s, 1H), 9.70-8.75 (v br, 2H), 8.08 (d, 2H), 7.99 (s, 1H), 7.93 (d, 1H), 7.65 (d, 1H), 7.57 (d, 2H), 7.45 (d, 1H), 7.40 (dd, 1H), 4.30-4.10 (m, 2H), 4.05-3.87 (m, 1H), 3.78 (s, 3H), 3.35-3.15 (m, 2H), 2.70 (s, 3H), 2.37 (s, 3H), 2.27-1.70 (m, 4H).

30

Example 4

N-[4-Methoxy-3-(1-methylazetidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

35

The title compound was prepared from 4-methoxy-3-(1-methylazetidin-2-ylmethoxy)aniline (D11) using the procedure of Example 1. Purification by chromatography on silica gel eluting with 5% methanol/chloroform followed by

crystallisation from ethyl acetate/60-80 petrol, afforded the title compound as a white solid (9%) m.pt. 160-161° C.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.14 (s, 1H), 8.02-7.89 (m, 4H), 7.50-7.38 (m, 3H), 7.32 (d, 1H), 7.12 (dd, 1H), 6.83 (d, 1H), 4.05 (d, 2H), 3.83 (s, 3H), 3.50-3.38 (m, 2H), 2.90-2.77 (m, 1H), 2.67 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 2.14-1.95 (m, 2H).

Example 5

N-[3-(Azetidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide hydrochloride

A solution of N-[3-(1-tert.-butoxycarbonylazetidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (D12, 0.47g, 0.80 mmol) in methanol (30 ml) was treated with 1M HCl in ether (2 ml) and stirred at room temp. for 20 h, followed by heating under reflux for 2 h. The solution was concentrated *in vacuo* and the residue crystallised from acetone/ether to afford the title compound as a white solid (39%) m. pt. 144-147° C.

¹H NMR (250 MHz, d⁶DMSO) δ (ppm): 10.35 (s, 1H), 9.60 (br s, 1H), 9.30 (br s, 1H), 8.10 (d, 2H), 7.98 (s, 1H), 7.92 (dd, 1H), 7.68 (d, 1H), 7.57 (d, 2H), 7.48-7.38 (m, 2H), 7.02 (d, 1H), 4.72 (br s, 1H), 4.50-4.36 (m, 1H), 4.30-4.20 (m, 1H), 4.00-3.84 (m, 2H), 3.79 (s, 3H), 2.69 (s, 3H), 2.60-2.25 (m, 2H), 2.36 (s, 3H).

Example 6

N-[4-Methoxy-3-(1-methylpiperidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

4-Methoxy-3-(1-methylpiperidin-2-ylmethoxy)aniline (D14, 0.160g, 0.640 mmol) was converted to give the title compound (0.040g, 12%) as a colourless oil according to the method of example 9, and was subsequently converted to its oxalate salt, m.pt. 117-119°C.

¹H NMR (250 MHz, CDCl₃) (free base) δ (ppm): 7.98 (m, 5H), 7.48 (m, 3H), 7.35 (d, 1H), 7.12 (dd, 1H), 6.98 (d, 1H), 4.23 (dd, 1H), 4.05 (dd, 1H), 3.83 (s, 3H), 3.00 (m, 1H), 2.70 (s, 3H), 2.55 (m, 1H), 2.50 (s, 3H), 2.33 (s, 3H), 2.28 (m, 1H), 1.95-1.55 (m, 5H), 1.40 (m, 1H).

Example 7

N-[4-Methoxy-3-(1-methylazepin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 5 4-Methoxy-3-(1-methylazepin-3-yloxy)aniline (D15, 0.195g, 0.780 mmol) was converted to give the title compound (0.158g, 30%) as a white foam according to the method of example 9, and was subsequently converted to its oxalate salt, m.pt. 110-113°C.

¹H NMR (250 MHz, CDCl₃) (free base) δ (ppm): 7.98 (m, 4H), 7.88 (s, 1H), 7.49 (d, 2H), 7.35 (d, 2H), 7.20 (dd, 1H), 6.90 (d, 1H), 4.52 (m, 1H), 3.88 (s, 3H), 2.97 (dd, 1H), 2.79 (m, 2H), 2.69 (s, 3H), 2.48 (m, 1H), 2.47 (s, 3H), 2.33 (s, 3H), 2.15 (m, 2H), 2.00-1.55 (m, 4H).

Example 8

- 15 **N-[4-Methoxy-3-(1-methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide**

4-Methoxy-3-(1-methylpiperidin-3-ylmethoxy)aniline (D17, 0.076g, 0.304 mmol) was converted to give the title compound (0.102g, 64%) as a white foam according to the method of example 9.

¹H NMR (250 MHz, CDCl₃) (free base) δ (ppm): 8.05-7.90 (m, 5H), 7.48 (d, 3H), 7.35 (d, 1H), 7.10 (dd, 1H), 6.90 (d, 1H), 3.91 (dd, 2H), 3.85 (s, 3H), 3.12 (m, 1H), 2.91 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 2.35 (m, 1H), 2.30 (s, 3H), 2.00 (m, 2H), 1.80 (m, 3H), 1.15 (m, 1H).

Example 9

N-[4-Methoxy-3-(1-methylpiperidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 30 2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (EP 0533268A1) (0.135g, 4.60 mmol) was suspended in thionyl chloride (5 ml) and was heated to reflux with stirring. After 1.5 h, the reaction mixture was allowed to cool and was evaporated under reduced pressure to give the crude acid chloride as a yellow solid which was
- 35 azeotroped with toluene and dried *in vacuo*. Meanwhile a solution of 4-methoxy-3-(1-methylpiperidin-3-yloxy)aniline (D19, 0.080g, 339 mmol) in dichloromethane (5 ml) was treated with triethylamine (0.047 ml, 3.39 mmol) followed by a solution of the crude acid chloride in dichloromethane (5 ml) added dropwise with stirring. After 20 h, the reaction

mixture was washed with water (1X) and sodium hydrogen carbonate solution (1X). The organic layer was then dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil. The oil was purified by silica-gel chromatography (9385, 6%, $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as eluant) to give the title compound as a colourless oil (0.084g, 49%), which was

5 converted to its oxalate salt, m.pt. 154-160°C.

^1H NMR (250 MHz, CDCl_3) (free base) δ (ppm): 8.02-7.90 (m, 5H), 7.48 (d, 2H), 7.40-7.25 (m, 3H), 6.90 (d, 1H), 4.45 (m, 1H), 3.87 (s, 3H), 3.10 (m, 1H), 2.71 (m, 1H), 2.69 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.30-2.04 (m, 3H), 1.90 (m, 1H), 1.80-1.50 (m, 2H).

10 Example 10

N-[4-Methoxy-3-(1-methylpyrrolidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

The title compound (0.38g, 45%) was prepared as a cream solid from 4-methoxy-3-(1-methylpyrrolidin-3-yloxy)aniline (D21, 0.38g, 0.0017 mol), using the method of Example 9.

15 ^1H NMR (250 MHz, d^6DMSO) δ (ppm): 8.11-7.82 (m, 5H), 7.58 (d, 2H), 7.49-7.32 (m, 3H), 6.96 (d, 1H), 4.87-4.72 (br s, 1H), 3.74 (s, 3H), 2.90-2.60 (m, 7H), 2.41-2.19 (m, 20 7H), 1.95-1.78 (m, 1H).

Example 11

N-[4-Methoxy-3-(3-quinuclidinyloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

25

The title compound was prepared from 4-methoxy-3-(3-quinuclidinyloxy)aniline (D23) using the procedure of Example 1. Purification by chromatography on silica gel eluting with 5% methanol/chloroform, followed by passage through a short basic alumina column eluting with ethyl acetate, afforded the title compound as a colourless oil. This was
30 converted to its oxalate salt and crystallised from a mixture of methanol/acetone/ether as a white solid (27%), m.pt. 110-113°C.

^1H NMR (200 MHz, CDCl_3) (free base) δ (ppm): 8.58 (s, 1H), 7.90-7.78 (m, 4H), 7.37 (d, 1H), 7.26 (d, 2H), 7.18 (d, 1H), 7.00 (dd, 1H), 6.73 (d, 1H), 4.32-4.20 (m, 1H), 3.72 (s, 3H), 3.22-3.02 (m, 1H), 2.95-2.45 (m, 5H), 2.55 (s, 3H), 2.18 (s, 3H), 2.12-1.85 (m, 35 2H), 1.67-1.50 (m, 1H), 1.47-1.10 (m, 2H).

Example 12

N-[4-Methoxy-3-(quinuclidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 5 A procedure, similar to that given in Example 1 was used to give the title product as a white powder (90%) from 4-methoxy-3-(quinuclidin-2-ylmethoxy)aniline (D25), m.pt. 235-240° C.

10 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.79 (1H, s), 8.12 (2H, d), 8.0-7.95 (2H, m), 7.78 (1H, dd), 7.60 (1H, d), 7.45 (2H, d), 7.32 (1H, d), 6.88 (1H, d), 4.62 (1H, dd), 4.35 (1H, dd), 3.81 (3H, s), 3.72 (2H, m), 3.48-3.10 (3H, m), 2.70 (3H, s), 2.35 (3H, s), 2.28 (1H, m), 2.12-1.80 (6H, m).

Example 13

- 15 **N-[4-Chloro-3-(1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide**

2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (EP 0533268 A1) (200 mg, 0.68 mmol) was suspended in thionyl chloride (5 ml) and was heated to reflux
20 with stirring. After 1 h, the reaction mixture was allowed to cool and was evaporated under reduced pressure to give the crude acid chloride as a yellow solid which was azeotroped with toluene and dried *in vacuo*. Meanwhile a solution of 4-chloro-3-(1-methylpyrrolidin-2-ylmethoxy)aniline (D29, 163 mg, 0.68 mmol) in dry tetrahydrofuran (10 ml) was treated with a solution of sodium hydroxide (54 mg) in water (½ ml),
25 followed by a solution of the crude acid chloride in dry tetrahydrofuran (10 ml), added dropwise with stirring. After 20 h, the reaction mixture was evaporated under reduced pressure and the residue partitioned between Na₂CO₃ and ethyl acetate. The organic layer was then dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by flash silica-gel chromatography using methanol and chloroform as eluant, to
30 give the title compound as a white solid (210 mg, 60%), m.pt. 191-193°C.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 8.05-7.88 (m, 5H), 7.66 (s, 1H), 7.47 (d, 2H), 7.38-7.24 (m, 2H), 6.99 (d, 1H), 4.05 (d, 2H), 3.12 (t, 1H), 2.89-2.63 (m, 4H), 2.57 (s, 3H), 2.44-2.26 (m, 4H), 2.15-1.65 (m, 4H).

35

Example 14

N-[4-(1-Methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 5 The title compound was prepared from 4-(1-methylpiperidin-3-ylmethoxy)aniline (D31) using the method of Example 1. Recrystallisation from ethyl acetate/petroleum ether gave a white solid (0.18g, 36%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.10-7.79 (m, 5H), 7.55 (d, 2H), 7.45 (d, 2H), 7.35 (d, 1H), 6.90 (d, 2H), 3.95-3.72 (m, 2H), 2.98 (br d, 1H), 2.29 (br d, 1H), 2.70 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H), 2.25-2.08 (m, 1H), 2.05-1.57 (m, 5H), 1.22-1.00 (m, 1H)

Example 15

- 15 **5-Chloro-2,3-dihydro-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(1-methylpyrrolidin-2-ylmethoxy)-1H-indole**

The title compound was prepared from 5-chloro-2,3-dihydro-6-(1-methylpyrrolidin-2-ylmethoxy)-1H-indole (D34) using the procedure of Example 13. Purification by chromatography on silica gel eluting with methanol/chloroform afforded the title compound as an off-white foam (10%) which was converted to the oxalate salt, m.pt. 102-105° C.

¹H NMR (250 MHz, (CD₃)₂CO) δ (ppm): 8.02 (s, 1H), 7.96 (d, 1H), 7.74 (d, 2H), 7.56 (d, 2H), 7.45 (d, 1H), 7.27 (s, 1H), 4.2 (t, 2H), 4.05-3.75 (m, 2H), 3.11 (t, 2H), 3.01 (t, 1H), 2.77-2.62 (m, 4H), 2.47 (s, 3H), 2.41 (s, 3H), 2.33-2.2 (m, 1H), 2.1-1.99 (m, 1H), 1.84-1.6 (m, 3H). (one aromatic proton not observed)

Example 16

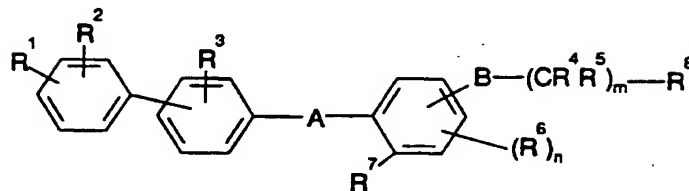
- 30 **2,3-Dihydro-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-[2-(1-methylpyrrolidin-2-yl)ethyl]-1H-indole**

The title compound (0.067g, 25%) was prepared from 2,3-dihydro-5-methoxy-6-(2-(1-methylpyrrolidin-2-yl)ethyl)-1H-indole (D43) (0.13g, 0.5 mmol) using the method of Example 1.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 8.00 (m, 3H), 7.62 (d, 2H), 7.50-7.30 (m, 3H), 6.75 (s, 1H), 4.13 (b, 2H), 3.82 (s, 3H), 3.48 (s, 3H), 3.12 (t, 2H), 2.69 (s, 3H), 2.38 (s, 3H), 2.12-1.50 (bm, 11H)

CLAIMS:

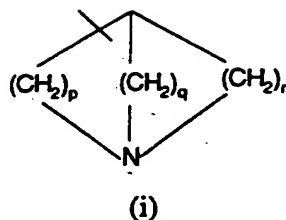
1. A compound of formula (I) or a salt thereof:



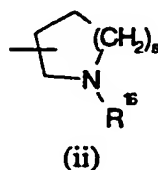
(I)

- 10 in which
 A is CONR where R is hydrogen or C₁₋₆alkyl;
 B is oxygen, S(O)_q where q is 0, 1 or 2, or B is NR¹⁰ where R¹⁰ is hydrogen or
 C₁₋₆alkyl or B is CH₂ when R⁷ and R form a group D;
 R¹ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy,
 15 hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, acyl, nitro,
 trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹⁰R¹¹, CO₂R¹⁰, CONR¹⁰R¹¹,
 CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)_aCO₂R¹¹, (CH₂)_aNR¹⁰R¹¹, (CH₂)_aCONR¹⁰R¹¹,
 (CH₂)_aNR¹⁰COR¹¹, (CH₂)_aCO₂C₁₋₆alkyl, CO₂(CH₂)_aOR¹⁰, NR¹⁰R¹¹,
 NR¹⁰CO₂R¹¹, NR¹⁰CONR¹⁰R¹¹, CR¹⁰=NOR¹¹, CNR¹⁰=NOR¹¹, where R¹⁰ and R¹¹
 20 are independently hydrogen or C₁₋₆alkyl and a is 1 to 4 or R¹ is an optionally substituted
 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen,
 nitrogen or sulphur;
 R² and R³ are independently hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl,
 C₃₋₆cycloalkenyl, C₁₋₆alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano,
 25 CO₂R¹¹, CONR¹²R¹³, NR¹²R¹³ where R¹¹, R¹³ and R¹³ are independently hydrogen
 or C₁₋₆alkyl;
 R⁴ and R⁵ are independently hydrogen or C₁₋₆alkyl;
 R⁶ is hydrogen, halogen, hydroxy, C₁₋₆alkyl or C₁₋₆alkoxy;
 R⁷ is hydrogen or together with R forms a group D where D is CR¹⁴=CR¹⁵,
 30 CR¹⁴=CR¹⁵CR¹⁴R¹⁵ or (CR¹⁴R¹⁵)_b where b is 2 or 3 and R¹⁴ and R¹⁵ are
 independently hydrogen or C₁₋₆alkyl;
 m is 0, 1, 2 or 3;
 n is 1 or 2; and
 R⁸ is a group of formula (i):

35

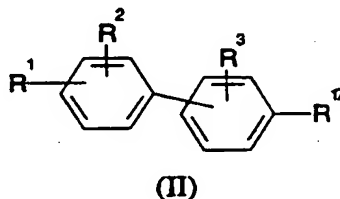


- where p, q and r are independently integers having the value 1, 2 or 3;
 5 or R⁸ is a group of formula (ii):

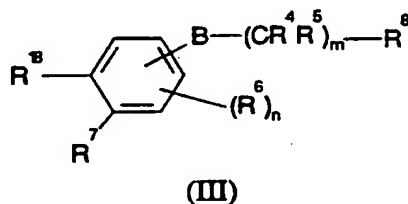


- 10 where s is 0, 1, 2 or 3 and R¹⁶ is hydrogen or C₁₋₆alkyl.
2. A compound according to claim 1 in which R¹ is oxadiazole.
 3. A compound according to claim 1 or 2 in which R² is C₁₋₆alkyl.
 4. A compound according to any one of claims 1 to 3 in which R³ is hydrogen
 5. A compound according to any one of claims 1 to 4 in which A is CONH and
 - 15 B is oxygen.
 6. A compound according to any one of claims 1 to 5 in which m is 1 and p is 1.
 7. A compound according to any one of claim 1 which R⁶ is C₁₋₆alkoxy.
 8. A compound according to claim 1 which is:
- N-[3-((S)-1-Methylpyrrolidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 20 N-[4-Methoxy-3-((R)-1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[4-Methoxy-3-((R)-pyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 25 N-[4-Methoxy-3-(1-methylazetidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[3-(Azetidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[4-Methoxy-3-(1-methylpiperidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 30 N-[4-Methoxy-3-(1-methylazepin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

- N-[4-Methoxy-3-(1-methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(1-methylpiperidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 5 N-[4-Methoxy-3-(1-methylpyrrolidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(3-quinuclidinyloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-Methoxy-3-(quinuclidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 10 N-[4-Chloro-3-(1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 N-[4-(1-Methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
 15 5-Chloro-2,3-dihydro-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(1-methylpyrrolidin-2-ylmethoxy)-1H-indole,
 2,3-Dihydro-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-[2-(1-methylpyrrolidin-2-yl)ethyl]-1H-indole,
 and pharmaceutically acceptable salts thereof.
- 20 9. A process for the preparation of a compound of formula (I) which comprises
 (a) for compounds where A is an amide linkage CONR⁹ reaction of a
 compound of formula (II):

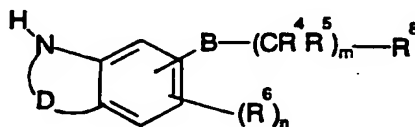


with a compound of formula (III):



wherein B, m, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined in formula (I) and R¹⁷ and R¹⁸ contain the appropriate functional group(s) necessary to form the A moiety; or

(b) where R^7 together with R^9 forms a group D reaction of a compound of formula (II) as defined above with a compound of formula (IV):



5

(IV)

wherein B, D, m, n, R^4 , R^5 , R^6 and R^8 are as defined in formula (I);

10 and optionally after (a) or (b) in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

10. A compound according to any one of claims 1 to 7 for use in therapy.

11. A pharmaceutical composition which comprises a compound according to

15 any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/01578

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D413/12 A61K31/41 C07D453/02 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 533 268 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see claims ---	1-7, 10, 11
A	EP,A,0 533 267 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see claims -----	1, 10, 11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * "&" document member of the same patent family

Date of the actual completion of the international search

9 August 1995

Date of mailing of the international search report

18. 08. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+ 31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 95/01578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-533268	24-03-93	AP-A- 303	28-01-94
		AU-B- 656021	19-01-95
		AU-A- 2453092	25-03-93
		CA-A- 2078505	19-03-93
		HU-A- 65608	28-07-94
		JP-A- 6116251	26-04-94
		NZ-A- 244373	28-03-95
		US-A- 5340810	23-08-94
		ZA-A- 9207108	08-09-93
		CN-A- 1076195	15-09-93
EP-A-533267	24-03-93	AU-A- 2452892	25-03-93
		AU-A- 2568792	27-04-93
		CA-A- 2078507	19-03-93
		CN-A- 1073430	23-06-93
		CZ-A- 9400611	16-11-94
		WO-A- 9306084	01-04-93
		FI-A- 941261	17-03-94
		JP-A- 6107637	19-04-94
		NO-A- 940974	17-03-94
		US-A- 5358948	25-10-94